REMARKS/ARGUMENTS

The Status of the Claims.

Claims 1-22, 24-50, and 58 are pending with entry of this response. Claims 1, 25, and 58 are amended herein. Support for the amendments is found throughout the specification as filed. For example, paragraph 143 describes how multiple nucleic acids generated from a biological sample are deposited onto a microarray such that each sample has a single unique location comprising multiple nucleic acids. This is further exemplified by paragraph 209 describing the level of multiplexing of which the claimed invention is capable. These advantages are further described in paragraph 71 and illustrated by Figure 1. These amendments introduce no new matter and entry of the amendments is respectfully requested.

35 U.S.C. §103(a)

The independent claims were rejected under 35 U.S.C. §103(a) as allegedly obvious over Dooley, in view of Lockhart and Porkka. The Examiner also rejected dependent claims under 35 U.S.C. §103(a) over Dooley and further in view of various combinations of Lockhart, Porkka, Cho, Nilsen, and Shuber. Applicant respectfully traverses.

A finding of obviousness requires a determination of whether "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 USC § 103(a). As the Federal Circuit has repeatedly indicated, this inquiry ultimately involves determining "whether a person of ordinary skill would have been motivated to combine the prior art to achieve the claimed invention and whether there would have been a reasonable expectation of success in doing so." *Dystar Textilfarben GmbH v. C.H. Patrick Co.* 80 USPQ2d 1641 at 1645 (Fed. Cir. 2006). The determination of the questions of motivation and expectation of success are based upon a four part factual inquiry:

(1) the scope and content of the prior art;

(2) the differences between the claimed invention and the prior art;

(3) the level of ordinary skill in the art; and,

(4) consideration of secondary indicia of non-obviousness.

Dystar, id, quoting *Graham v. John Deere Co.,* 383 US 1, 17 [148 USPQ 459] (S. Ct. 1966).

In the Office Action mailed April7, 2008, the remaining issue appears to be whether the prior art teaches a sample comprising multiple nucleic acids species arrayed at a single location on an array, e.g., allowing the simultaneous analysis of multiple samples for multiple genes. The action specifies that Dooley, not Porkka, is cited for a teaching regarding multiple samples. As described below, any alleged teaching in Dooley regarding multiple samples does not teach a sample comprising multiple nucleic acids species arrayed at a single address on an array as claimed and therefore cannot render the claimed invention obvious.

Although Applicant believes that the claims clearly state such already, Applicant herein amends independent claims 1, 25, and 58 to specify that each sample is deposited at a single location on the array. It is also abundantly clear from the claims that each sample comprises multiple nucleic acid species. This amendment is made solely for the purpose of advancing prosecution and without acquiescing to any rejection.

The scope and content of the prior art

The combination of references does not render the claimed invention obvious because it fails to teach the elements of the claim. Complete consideration of the Graham factors and the legal standards of motivation and expectation of success clearly establish the *non-obvious* nature of the invention.

The Elements Of The Claim Are Not Taught In The Combination Of References

In considering the scope and content of the prior art, a first basic requirement for establishing obviousness is that the combination of references must actually teach all of the elements of the claims. MPEP 2143.03. The combination of references in the rejection fails to meet this most basic factual requirement for establishing obviousness.

The references, when considered individually or together, fail to teach at least one main element of the claimed invention, e.g., the placement of a sample containing multiple nucleic acids species at a single array location. It is explicitly stated in step (c) of the claimed methods that each nucleic acid sample comprises a plurality of different nucleic acid species and in step (d) that each sample is deposited onto a unique location on the array. This method allows the identification of multiple nucleic acid species in multiple samples simultaneously on a single array.

In the prior art, arrays are constructed with a single species, e.g., a probe or a nucleic acid to be detected, at each addressable location on the array. None of the references cited contain multiple species at a single array address. Therefore, the references do not teach every element of the claimed invention.

The rejection alleges that these elements are taught in the prior art, by pointing to the fact that Dooley discusses multiple samples. (The rejection concedes that Porkka does not teach this element of the claims.) However, when Dooley discusses different samples, e.g., in column 8, lines 55-64 or in Figure 1, it is in the context of a comparison of different samples that have been individually tested, e.g., each sample has been separately probed, e.g., one sample per array, not simultaneously probed on the same array as claimed.

When viewed as a whole, the concepts of Dooley do not even begin to describe the claimed invention. If anything, they describe a step that could be used in the claimed invention, e.g., to select a set of nucleic acids to be used in a probe set. A key inventive concept in the claimed invention is the combination of multiple nucleic acids at a single array address. Although Dooley uses multiple samples, they are not arrayed on a single array wherein each location contains multiple nucleic acid species as in the claimed invention. Each sample in Dooley is allotted its own array, wherein each sample in the claimed invention is allotted one spot on an array. In the claimed invention, the methods used to generate the samples, the use of defined sequence probes, and the non-traditional array format combine to provide a level of multiplexing not available in Dooley, Porkka and/or Lockhart.

No Specific Motivation for the Combination Exists

Even if many of the individual elements of the claims could be found in the prior art as well as the desire to analyze more compounds faster and more efficiently, the art must contain some suggestion or motivation to combine these elements in the manner claimed. The Supreme Court recently reaffirmed the factual analysis established in *Graham v. John Deere Co.*, cautioning that the question of motivation to combine the prior art must be approached with "common sense," rather than as a rigid formula:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

KSR International Co. V. Teleflex inc. et al. 550 U. S. ____ (2007) slip opinion page 6. The universe of possibilities is huge regarding possible changes to array technology and therefore some specific suggestion must be presented as to why one of skill would have selected this particular combination claimed from the infinite possible solutions.

The Office alleged that one of skill would be motivated by cost-effectiveness to use the informative array of Dooley with the array method of Porkka, e.g., the immobilization of genes to be identified on the array. The Office alleged that this would be advantageous to one of skill in the art because it would reduce the number of gene sequences on the array. While it may be true that one of skill in the art would be motivated by cost-effectiveness to decrease the number of genes on the array, that is not the point of the claimed invention. The claimed invention increases the number of samples that may be analyzed on a single array. This is a different alternative to the cost problem, e.g., arrived at by depositing multiple nucleic acids at each spot on the array, than the one arrived at by any alleged combination of Dooley and Porkka. Therefore, the motivation alleged in the rejection does not apply to the claimed invention.

If one's motivation to combine the two references is to increase the throughput of compound screening, then one would not achieve very much with the combination of Porkka and Dooley because neither teaches how to manage the screening of multiple samples per array. Although it is asserted that Porkka flips the array, it still puts only one nucleic acid species on each spot on the array. The array format of Porkka, even if

reversed as claimed and used with the informative arrays of Dooley, does not provide the same benefit as the claimed invention. It merely provides a flipped array that can be screened using a smaller group of selected probes. Therefore, because the combination of Dooley and Porkka does not provide the same advantages as the claimed invention, the question of motivation becomes moot.

Furthermore, Applicants question why, given the skill in the art and vast amount of prior art available in gene expression analysis, this technique was not done before if it was obvious as alleged by the Examiner. What is obvious is that those of skill in the art have long been searching for techniques to multiplex and examine multiple genes in multiple samples faster and more efficiently. However, no one came upon this solution until Applicant. Therefore, the claimed invention is non-obvious.

The differences between the claimed invention and the prior art

The second Graham factor relates to the differences between the claimed invention and the prior art. In this case, the differences are significant enough that a rejection for obviousness cannot be upheld.

The claimed invention places a plurality of nucleic acid species at a single array address to analyze multiple genes simultaneously in multiple samples, e.g., each nucleic acid sample represents the total expressed RNA from a single biological sample. The prior art, e.g., either Dooley or Porkka, arrays a single nucleic acid species at each address, e.g., the entire array is used to analyze the expression products of a single sample. The claimed invention allows several genes from each of a plurality of samples, e.g., 1536 different samples, to be analyzed simultaneously for multiple genes on a single array. To do this using the techniques of any of the cited references, would require 1536 different arrays. Therefore, the claimed invention achieves a level of throughput and efficiency not even hinted at in the prior art. Dooley presents a system to reduce the number of genes that are analyzed and perhaps this would allow two samples to be placed on the same array, but they would not be arrayed as claimed, e.g., with a single sample comprising multiple nucleic acids at a single spot on the array.

In Dooley *et al.*, the actual RNA sample (or, *e.g.*, corresponding cDNA or other amplified product) remains in the soluble phase and is used to hybridize to an array of

probes. In contrast, the present invention uses nucleic acids physically derived from and corresponding to the RNA samples to construct an array. In Dooley, the actual sample comprising multiple nucleic acids is applied to the array in the soluable phase, e.g., one sample to each array with one nucleic acid species at each location. In the present invention each sample is applied to a particular array position and each sample comprises multiple nucleic acid species. Therefore, there are multiple nucleic acid species at each array address. This is not shown in the prior art. If the techniques alleged to be taught by Porkka are added to the arrays of Dooley, one may arrive at a probe set applied in the soluable phase to an array with multiple nucleic acids arrayed thereon. However, the nucleic acids are arrayed with one nucleic acid per location, not one sample comprising multiple nucleic acids at each location on the array.

Therefore, one important difference between the claimed invention and the prior art is that the claimed invention provides multiple sample on a single array that can be used, e.g., with a single probes set to simultaneously analyze multiple samples for multiple genes with a single probe set. This has not been done in the prior art and the combination provided by the Office does not result in this level of multiplexing.

Neither an individual reference nor the combination of references cited in the rejection provide the level of multiplexing provided by the claimed methods. The set of probes and the method of arraying the expression products of a plurality of samples are different from those presented in the prior art or any combination of prior art presented in the Action.

The level of skill in the art

While the level of skill in the prior art is quite extensive, the idea of arraying multiple nucleic acid species at a single address in the reversed array format in the manner claimed was non-existent in the art. In fact, such a method is only available when the multiple techniques used in the claimed invention are combined in the same manner as claimed.

No Expectation of Success Existed at the Time of the Invention for the Proposed Combination

At the time of the invention, no expectation of success existed for the claimed combination of references to produce the claimed invention. In fact, one reason such a

combination would not work is that every element of the claimed method is not present in the prior art.

The array format in either Dooley or Porkka, even if reversed so that the probe is in the soluable phase, does not work as the claimed invention does because it does not deposit multiple nucleic acid species on a single addressable location of the array and then probe the array with a set of probes comprising different detectable labels. Therefore, even if one were motivated to combine the two references, one would not have any expectation of success regarding increased throughput with the methods of Porkka and Dooley combined. For example, if Dooley and Porkka were combined as suggested in the rejection, it would result in a reversed array for use with an informative group of probes. The reversal **would not** result in multiple nucleic acids at each location on the array and therefore would not have the throughput capacity of the claimed method. The claimed invention allows a vast increase in throughput over the art, individually or combined.

The addition of Lockhart, Cho, Nilsen, and/or Shuber fails to remedy the above defects in the rejection as none of them are even alleged to teach the lacking elements. Therefore, the rejections of the dependent claims should be withdrawn for the same reasons as stated above.

In conclusion, the prior art does not teach every element of the claimed invention and therefore any motivation to combine the references is moot and any expectation of success for the combination of references is inapplicable because it would result in an entirely different method than that claimed. Upon consideration of the Graham factors, it is clear that the differences between the prior art and the claimed invention are too great to support a rejection based on obviousness. In view of the arguments above, Applicant asserts that the claims are non-obvious and respectfully request that the rejection be withdrawn.

CONCLUSION

In view of the foregoing, Applicant believes that all claims now pending in this application are in condition for allowance. If the Examiner believes there are any remaining issues regarding the patentability of the pending claims, the Examiner is

encouraged to contact the undersigned by telephone to expedite the issuance of a Notice of Allowance.

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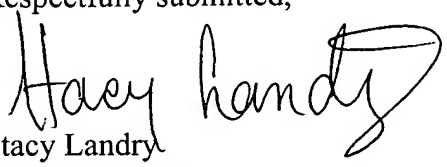
Respectfully submitted,



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Attachments:

1) A transmittal sheet; and
2) A receipt indication postcard.